Registry / ChemAbs Search of cmpds 1/23/2004

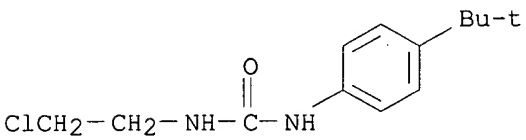
09/741,814

L8 ANSWER 1 OF 6 CA COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 140:4826 CA
TITLE: A New Generation of N-Aryl-N'-(1-alkyl-2-chloroethyl)ureas as Microtubule Disrupters: Synthesis, Antiproliferative Activity, and .beta.-**Tubulin** Alkylation Kinetics
AUTHOR(S): Mounetou, Emmanuelle; Legault, Jean; Lacroix, Jacques; Gaudreault, Rene C.
CORPORATE SOURCE: Centre de recherche CHUQ, Hopital Saint-Francois d'Assise, Quebec, QC, G1L3L5, Can.
SOURCE: Journal of Medicinal Chemistry (2003), 46(23), 5055-5063
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

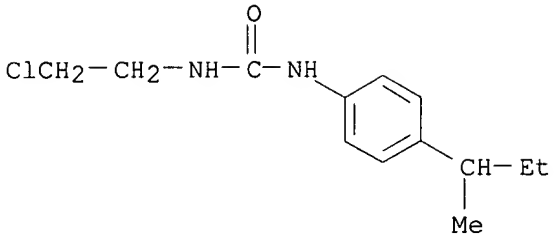
AB New N-aryl-N'-2-chloroethyl ureas (CEUs) R1NHCONHCHR2CH2Cl [R1 = 4-IC6H4, 4-(Me2CH)C6H4, 4-Me3CC6H4, 4-(EtCHMe)C6H4, 2-naphthyl, 2-fluorenyl, 5-indanyl; R2 = Me, Et; (I)] with enhanced cytotoxicity were developed as antimitotic agents potentially useful in cancer chemotherapy. Highly potent CEUs were obtained by introduction of a branched alkylating chain, the N'-(1-methyl-2-chloro)ethyl group. Their cytotoxic activity was enantio-dependent and induced through specific alkylation of .beta.-**tubulin**, leading to microtubule disruption and mitotic arrest. Overall, the structural modifications of the CEUs described here significantly improved their kinetics of .beta.-**tubulin** alkylation. Two of the compds. of this new series, (R)-I [R1 = 4-IC6H4, 4-(Me2CH)C6H4; R2 = Me], displayed particularly enhanced antiproliferative activity related to a faster reaction with .beta.-**tubulin** and merit further investigation as potential antitumor agents.

IT **118202-59-8 161194-45-2 161194-47-4**
RL: PAC (Pharmacological activity); BIOL (Biological study)
(prepn. of aryl(chloroalkyl) ureas as microtubule disrupters, their antiproliferative activity and .beta.-**tubulin** alkylation kinetics)

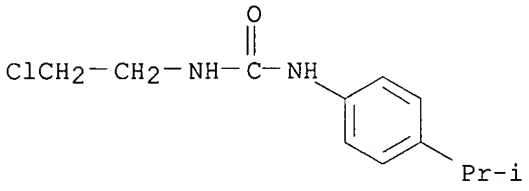
RN 118202-59-8 CA
CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-45-2 CA
CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylpropyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-47-4 CA
CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylethyl)phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

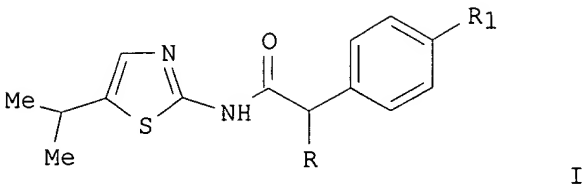
L8 ANSWER 2 OF 6 CA COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 138:137299 CA
TITLE: Preparation of phenylacetamido-thiazole derivatives as antitumor agents
INVENTOR(S): Pevarello, Paolo; Amici, Raffaella; Villa, Manuela; Salom, Barbara; Vulpetti, Anna; Varasi, Mario; Brasca, Maria Gabriella; Traquandi, Gabriella; Nesi, Marcella
PATENT ASSIGNEE(S): Pharmacia Italia S.P.A., Italy
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003008365	A2	20030130	WO 2002-EP7289	20020702

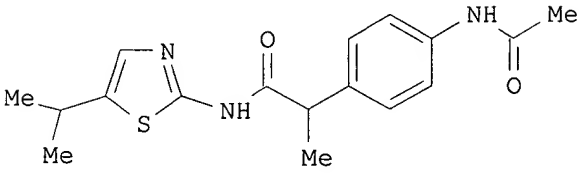
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-907947 A 20010719
US 2002-357642P P 20020220
OTHER SOURCE(S): MARPAT 138:137299

GI



I



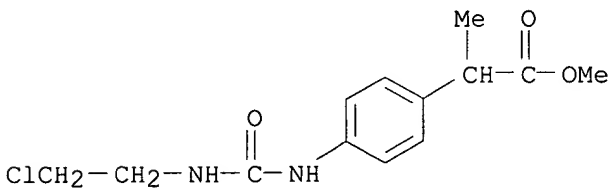
II

AB Phenylacetamido-thiazole derivs. [I; wherein R = H, (C1-C4)alkyl; R1 = 5-membered heterocycle contg. 1 or 2 heteroatoms selected from O and N, or amido group] were prepd. For example, (2S)-2-[4-(acetamido)phenyl]-N-(5-isopropyl-1,3-thiazol-2-yl)propanamide [2(S)-(II)] was prepd. by the provided method. The compds. are active as cdk/cyclin inhibitors and, thus, are useful for treating cell proliferative disorders assocd. with an altered cell dependent kinase activity. The proliferative disorders include cancer and a wide variety of other conditions, such as Alzheimer's disease, viral infections, autoimmune diseases, and neurodegenerative disorders. For example, compd. II, when tested against cdk2/cyclin A, showed an inhibitory activity, expressed as IC50, of 11 nM.

IT **492445-78-0P**, Methyl 2-[4-([[(2-chloroethyl)amino]carbonyl]amino)phenyl]propanoate **492445-79-1P**, Methyl (2R)-2-[4-([[(2-chloroethyl)amino]carbonyl]amino)phenyl]propanoate **492445-80-4P**, Methyl (2S)-2-[4-([[(2-chloroethyl)amino]carbonyl]amino)phenyl]propanoate
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of phenylacetamido-thiazole derivs. as cdk/cyclin inhibitors)

RN 492445-78-0 CA

CN Benzeneacetic acid, 4-[[[(2-chloroethyl)amino]carbonyl]amino]-.alpha.-methyl-, methyl ester (9CI) (CA INDEX NAME)

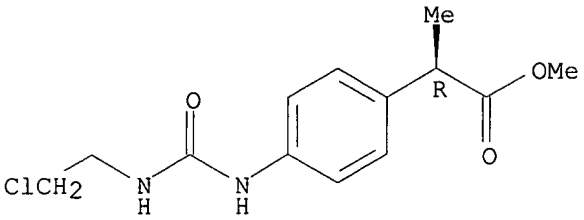


RN 492445-79-1 CA

CN Benzeneacetic acid, 4-[[[(2-chloroethyl)amino]carbonyl]amino]-.alpha.-

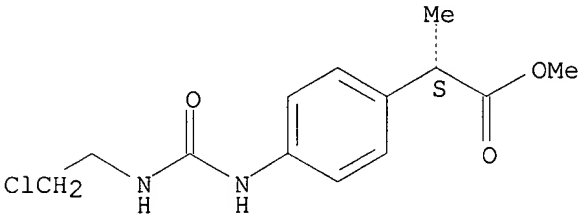
methyl-, methyl ester, (.alpha.R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 492445-80-4 CA
CN Benzeneacetic acid, 4-[[[(2-chloroethyl)amino]carbonyl]amino]-.alpha.-methyl-, methyl ester, (.alpha.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L8 ANSWER 3 OF 6 CA COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 135:71264 CA
TITLE: Carbamidobenzenes for use as antitumor .beta.-**tubulin** inhibitors
INVENTOR(S): Gaudreault, Rene C.; Legault, Jean
PATENT ASSIGNEE(S): Universite Laval, Can.
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001047504	A2	20010705	WO 2000-CA1579	20001222
WO 2001047504	A3	20020110		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

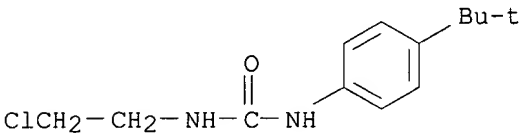
US 2002115722	A1	20020822	US 2000-741814	20001222

PRIORITY APPLN. INFO.: US 1999-171615P P 19991223

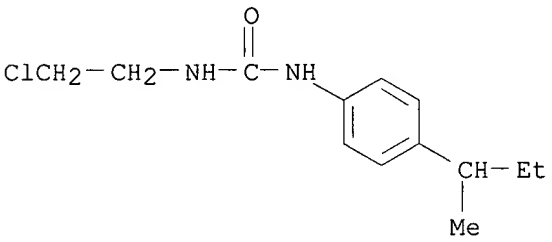
AB Disclosed herein are benzene carbamide .beta.-**tubulin** inhibitors, prodrugs thereof, and therapeutically acceptable salts thereof for use as anti-cancer cell proliferation agents.

IT **118202-59-8 161194-45-2 161194-47-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(carbamidobenzenes for use as antitumor .beta.-**tubulin** inhibitors)

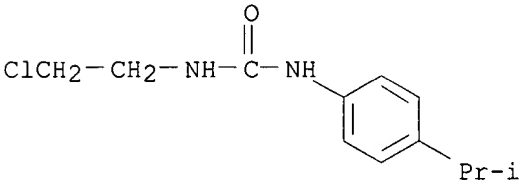
RN 118202-59-8 CA
CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-45-2 CA
CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylpropyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-47-4 CA
CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylethyl)phenyl]- (9CI) (CA INDEX NAME)



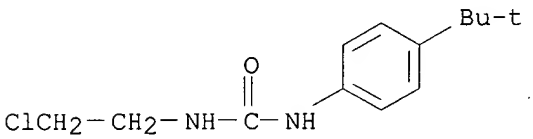
L8 ANSWER 4 OF 6 CA COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 134:246870 CA
TITLE: Antimitotic antitumor agents: synthesis, structure-activity relationships, and biological characterization of N-aryl-N'-(2-chloroethyl)ureas as new selective alkylating agents
AUTHOR(S): Mounetou, Emmanuelle; Legault, Jean; Lacroix, Jacques; C-Gaudreault, Rene
CORPORATE SOURCE: Centre de Recherche, CHUQ Hopital Saint-Francois d'Assise, QC, G1L3L5, Can.

SOURCE: Journal of Medicinal Chemistry (2001), 44(5), 694-702
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

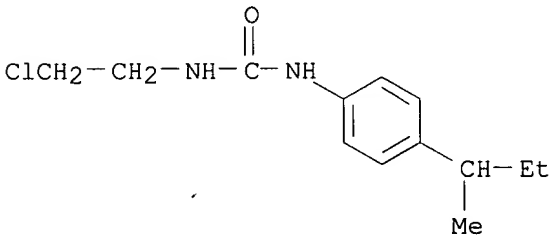
AB A series of N-aryl-N'-(2-chloroethyl) ureas (CEUs) and derivs. were synthesized and evaluated for antiproliferative activity against a wide panel of tumor cell lines. Systematic structure-activity relationship (SAR) studies indicated that: (i) a branched alkyl chain or a halogen at the 4-position of the Ph ring or a fluorenyl/indanyl group, (ii) an exocyclic urea function, and (iii) a N'-2-chloroethyl moiety were required to ensure significant cytotoxicity. Biol. expts., such as immunofluorescence microscopy, confirmed that these promising compds. alter the cytoskeleton by inducing microtubule depolymn. via selective alkylation of .beta.-**tubulin**. Subsequent evaluations demonstrated that potent CEUs were weak alkylators, were non-DNA-damaging agents, and did not interact with the thiol function of either glutathione or glutathione reductase. Therefore, CEUs are part of a new class of antimitotic agents. Finally, among the series of CEUs evaluated, compds. N' 4-isopropylphenyl,4-sec-butylphenyl, 4-tert-butylphenyl, and 4-iodophenyl N-(2-chloroethyl)ureas were selected for further in vivo trials.

IT **118202-59-8 161194-45-2 161194-47-4**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(synthesis, SAR, and biol. characterization of arylchloroethyl ureas as new selective alkylating agents)

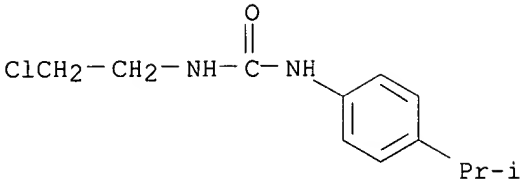
RN 118202-59-8 CA
CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-45-2 CA
CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylpropyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-47-4 CA
CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylethyl)phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

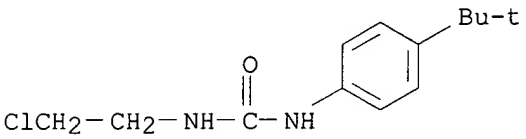
L8 ANSWER 5 OF 6 CA COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 132:302978 CA
TITLE: Microtubule disruption induced in vivo by alkylation of .beta.-**tubulin** by 1-aryl-3-(2-chloroethyl)ureas, a novel class of soft alkylating agents
AUTHOR(S): Legault, Jean; Gaulin, Jean-Francois; Mounetou, Emmanuelle; Bolduc, Sebastien; Lacroix, Jacques; Poyet, Patrick; Gaudreault, Rene C.
CORPORATE SOURCE: Biotechnology Unit, Biomaterial Institute of Quebec, Centre Hospitalier Universitaire de Quebec, Laval University, Quebec City, QC, G1L 3L5, Can.
SOURCE: Cancer Research (2000), 60(4), 985-992
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: AACR Subscription Office
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have previously reported that 4-tert-butyl-[3-(2-chloroethyl)ureido] benzene (4-tBCEU), a potent cytotoxic agent, modulates the synthesis of **tubulins**, suggesting that its cytotoxicity may be mediated through an antimicrotubule mechanism. Indeed, 4-t-BCEU and its 4-iso-Pr (4-iso-Pr [3-(2-chloroethyl)ureido] benzene) and 4-sec-Bu (4-sec-Bu [3-(2-chloroethyl)ureido] benzene) homologues induced disruption of the cytoskeleton and arrest of the cell cycle in G2 transition and mitosis. To better understand the mechanisms responsible for microtubule disruption by 1-aryl-3-(2-chloroethyl)ureas (CEU), we first examd. their cytotoxicity on Chinese hamster ovary cells resistant to vinblastine and colchicine due to the expression of mutated **tubulins** (CHO-VV 3-2). These cells showed resistance to CEU, e.g., 4-tBCEU having an IC50 of 21.3 .+-. 1.1 .mu.M as compared with an IC50 of 11.6 .+-. 0.7 .mu.M for wild-type cells, suggesting a direct effect of the drugs on **tubulins**. Western blot anal. confirmed the disruption of microtubules and evidenced the formation of an addnl. immunoreactive .beta.-**tubulin** with an apparent lower mol. wt. on SDS polyacrylamide gel. Incubation of MDA-MB-231 cells with [urea-14C]-4-tBCEU revealed the presence of a radioactive **protein** that coincided with the addnl. .beta.-**tubulin** band, indicating that CEU could covalently bind to the .beta.-**tubulin**. The 4-tBCEU-binding site on .beta.-**tubulin** was identified by competition of the CEU with colchicine, vinblastine, and iodoacetamide, a specific alkylating agent of sulfhydryl groups of cysteine residues. Colchicine, but not vinblastine, prevented the formation of the addnl. .beta.-**tubulin** band, suggesting that 4-tBCEU alkylates either Cys239 or Cys354 residues near the colchicine-binding site. To det. the cysteine residue alkylated by 4-tBCEU, we incubated the radiolabeled drug with human neuroblastoma cells (SK-N-SH) that overexpress the .beta.III-**tubulin**, an isoform where Cys239 is replaced by a serine residue. The results clearly showed

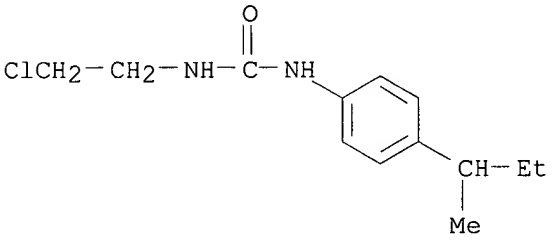
that .beta.III-**tubulin** is not alkylated by [urea-14C]-4-tBCEU, suggesting that cysteine 239 residue is essential for the reactivity of 4-tBCEU with .beta.-**tubulin**. Taken together, these findings indicate that the mechanism of cytotoxicity of CEU involves microtubule depolymn. through alkylation of .beta.-**tubulin**.

IT **118202-59-8 161194-45-2 161194-47-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(microtubule disruption induced by .beta.-**tubulin** alkylation by 1-aryl-3-(2-chloroethyl)ureas, novel class of soft alkylating agents)

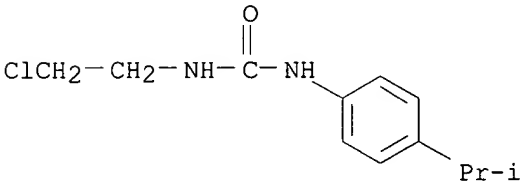
RN 118202-59-8 CA
CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-45-2 CA
CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylpropyl)phenyl]- (9CI) (CA INDEX NAME)



RN 161194-47-4 CA
CN Urea, N-(2-chloroethyl)-N'-[4-(1-methylethyl)phenyl]- (9CI) (CA INDEX NAME)



L8 ANSWER 6 OF 6 CA COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 121:339 CA
TITLE: Effect of an aryl chloroethyl urea on **tubulin** and vimentin syntheses in a human breast cancer cell line
AUTHOR(S): Poyet, Patrick; Ritchot, Nathalie; Bechard, Philippe; Gaudreault, Rene C.

CORPORATE SOURCE: Cent. Rech., Hop. Saint - Francois d'Assise, Quebec, QC, G1L 3L5, Can.
SOURCE: Anticancer Research (1993), 13(5A), 1447-52
CODEN: ANTRD4; ISSN: 0250-7005
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new class of antineoplastic agents, 1-aryl-3-(2-chloroethyl)ureas (CEUs), was recently developed in the authors' lab. To optimize the pharmacol. and the biol. properties of this new class of compds. and to det. its mechanism of action, at the cellular level, the authors studied the effect of 4-tert-Bu-[3-(2-chloroethyl)ureido]benzene (tBCEU) on MDA-MB-231, a human breast cancer hormone-independent cell line. The effect of tBCEU on **protein** synthesis and on the accumulation of specific mRNAs was evaluated. The results indicate that tBCEU increases the synthesis of at least two **proteins** present in the cytoskeleton: **tubulin** and vimentin. The effect of tBCEU on their transcripts indicates that tBCEU decreases the accumulation of **tubulin** and vimentin mRNA. These results suggest that the antineoplastic activity of tBCEU is in part related to an alteration in the synthesis pathway of **tubulin** and vimentin.

IT **118202-59-8**
RL: BIOL (Biological study)
(**tubulin** and vimentin formation inhibition by, in human breast cancer cell line, antitumor mechanism in relation to)

RN 118202-59-8 CA

CN Urea, N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl)phenyl]- (9CI) (CA INDEX NAME)